Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 1

Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations

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Background: The present article has been written to convey concepts of anaesthetic care within the context of an Enhanced Recovery After Surgery (ERAS) programme, thus aligning the practice of anaesthesia with the care delivered by the surgical team before, during and after surgery.
Methods: The physiological principles supporting the implementation of the ERAS programmes in patients undergoing major abdominal procedures are reviewed using an updated literature search and discussed by a multidisciplinary group composed of anaesthesiologists and surgeons with the aim to improve perioperative care.
Results: The pathophysiology of some key perioperative elements disturbing the homoeostatic mechanisms such as insulin resistance, ileus and pain is here discussed.
Conclusions: Evidence-based strategies aimed at controlling the disruption of homoeostasis need to be evaluated in the context of ERAS programmes. Anaesthesiologists could, therefore, play a crucial role in facilitating the recovery process.

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Editorial comment: what this article tells us
Complications after surgery are still a major problem. Enhanced Recovery after Surgery (ERAS) programmes may minimise some of the negative impact of surgery on organ function and this article describes the pathophysiology and the role of the anaesthesiologist in this context.

Despite steady advances in anaesthetic and surgical techniques over the years, post-operative complications remain one of the major drawbacks of surgery, not only for the specific patient involved but also for their surgical care team and the health care system in general. Rarely do patients die on the operating table during the surgical procedure, but rather from the pathophysiological response to surgery and its complications. The progressive understanding of the physiological basis of surgical injury has been the rationale underpinning the research efforts of interdisciplinary teams, incorporating surgeons, anaesthesiologists and nurses (among others) to minimise the surgical stress response and thereby improve outcomes. However, one of the immediate challenges to improve the quality of perioperative care is not to discover new knowledge, but rather to integrate what we already know into clinical practice. To this end, the concept of "fast-track surgery" was introduced in the 1990s by Henrik Kehlet. It was demonstrated that by applying evidence-based perioperative principles to open colonic surgery, the post-operative length of hospital stay could be reduced to 2–3 days.[1,2] Realising that the surgical journey involves many professional competencies, a more integrated, multiprofessional, multidisciplinary approach was needed, whereby a decision taken early in the course of the treatment plan would impact on later developments and influence the choices available for recovery further down the line. Unfortunately, large gaps still exist between what the evidence suggests should happen and what actually happens in practice.[1,3]

Compared with traditional perioperative care, the Enhanced Recovery After Surgery (ERAS) programme represents a fundamental shift in the process of care, by including multiple interventions that attenuate surgical stress, maintain physiological function and expedite return to baseline.[4] While each intervention has a small effect, all together they have a stronger synergistic impact (Fig. 1).

The ERAS Society recently published three guidelines on perioperative care focused on colonic,[5] rectal/pelvic[6] and pancreatic and gastric resection.[7] Previous versions of such guidelines have been shown to impact on daily practice.[4,8]

Gustafsson and coworkers[9] showed that with better compliance to an evidence-based ERAS protocol, outcomes improved: ERAS programme patients treated with less than 50% compliance had a complication rate of almost 50%, while those following the protocol more closely (90% compliance) had fewer than 20% complications. Similar improvements have been reported in a meta-analysis of randomised trials.[10]

The aim of this article was to review the pathophysiological basis of some key elements which form the basis of the ERAS programme. The second article, which follows, is more hands on and practical, and is meant to propose recommendations for anaesthetic protocols in the ERAS setting. Obviously, such an approach is based on best available evidence and should not to be seen as set in stone, as there are areas of challenge for the anaesthesiologist beside several aspects of controversial nature that require more research and development. The current papers are the joint effort of a wide range of professionals involved in the improvement of perioperative care working for the ERAS Society.

Methods

The present narrative review has been written following several meetings of a group of anaesthesiologists and surgeons, and after reviewing the literature between 1990 and 2014 on specific perioperative topics. The intention of the authors was to convey concepts of pathophysiology within the context of the ERAS programme, aligning the practice of anaesthesia with the

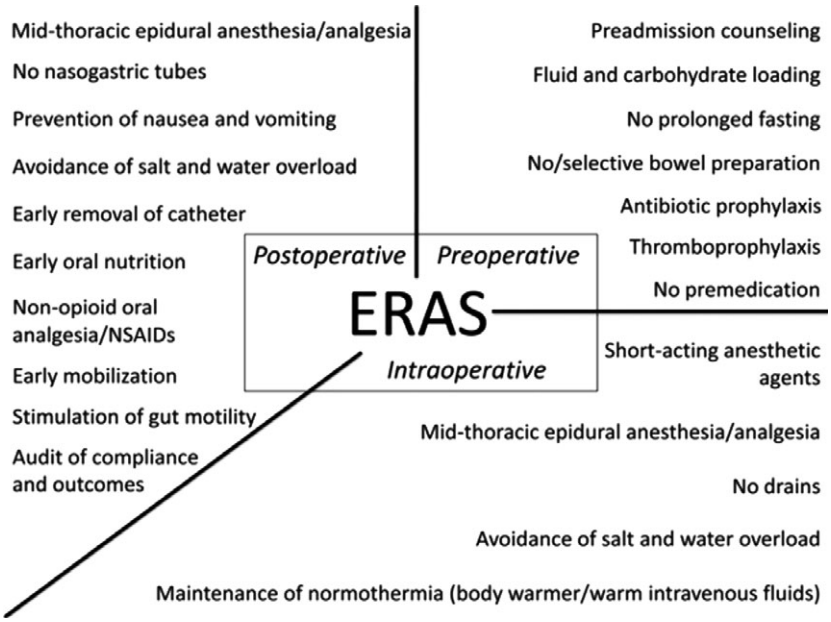

Fig. 1. ERAS elements. Reproduced from Varadhan KK et al. with permission.[105]

care delivered by the surgical team before, during and after surgery.

The role of the anaesthesiologist in implementing ERAS

Implementing ERAS programmes requires a multidisciplinary approach and within this philosophy, it is vital to avoid a 'silo mentality' and this applies most emphatically to the anaesthesia member of the team. Indeed in many institutes/countries, there is a drive towards anaesthesiologists fulfilling the role of perioperative physicians.

In the pre-operative phase, the anaesthesiologist may well run a formal pre-admission anaesthesia clinic for the assessment of patients deemed at high risk by either the surgeon or the pre-admission nurse. Activities may include formal risk assessment, optimisation or referral to other specialties such as cardiology or the frailty clinic. In the post-operative phase, the anaesthesiologist has a role in patient supervision in PACU/HDU to optimise opiate sparing, avoid excessive fluid loading and intervene early with complications such as delirium. Such a role can be extended onto the ward as a key member of the acute pain team. Finally, at a strategic level, the anaesthesiologist can contribute to team leadership, protocol compliance, audit and ongoing team education.

Preparing the patient for surgical stress

The world's population has increasing longevity, with average life expectancies rising yearly. A large proportion of the elderly population requires surgery for various reasons. The physiological changes associated with ageing are responsible for decreased reserve, impaired functional status, thus leading to poor capacity to withstand the stress of surgery. Co-morbidities associated with the elderly include hypertension, ischaemic heart disease, stroke, hypercholesterolaemia, chronic obstructive airway disease and diabetes. Although age per se does not preclude surgery, the presence of coexisting diseases has a greater impact on post-operative morbidity and mortality than age alone.[11] Furthermore, the burden of obesity, cancer and surgery represents a major stressor on organ systems with possible sequelae for cancer spread and declining functional ability. Smoking, alcohol, anaemia, poor nutritional status and poor glycaemic control can further impact adversely on post-operative infection rate, immune function and tissue healing. Preoperative anxiety, emotional distress and

depression have been shown to be associated with higher complication rates, greater post-operative pain, cognitive disturbances and delayed convalescence.

Fitness can be subdivided into coexisting medical problems and physical fitness. Pre-existing health factors such as myocardial infarction, heart failure, stroke, peripheral vascular disease and impaired kidney function can increase the risk of post-operative complications. There is also sufficient evidence that patients with poor physical conditions and low anaerobic threshold have greater post-operative morbidity and mortality.[12] In patients with cardiopulmonary disease, a 6-min walking distance (6MWD) < 350 m predicts mortality.[13] Similarly, in colorectal surgery patients, the 6MWD (which has a weak inverse correlation with sarcopenia) was found to correlate well with peak oxygen consumption in predicting post-operative cardiopulmonary complications.[14]

Risk assessment, optimisation of pre-existing organ function and education are essential ERAS elements for the preparation of patients facing surgery. The multidisciplinary team involved in the process includes anaesthesiologists, surgeons, internists, nutritionists, physiotherapists, nurses and, when needed, psychologists. Besides increasing physiological reserves and pharmacological optimisation, patients and caregivers need to be educated about the surgical process and empowered. The whole patient journey, starting with evaluation, then optimisation of physical, mental, nutritional functions (prehabilitation), then moving through surgery and the hospital episode and finishing with recovery, should be explained well in advance to facilitate active participation, comprehension and allay anxiety. Ideally audiovisual material should be made available. As patient expectation plays a role in determining post-operative outcome, clear information about the process of care has to be delivered to caregivers as well as the patients.[15]

Why it is important to control surgical stress and maintain homoeostasis

For every action, there is a reaction and the reaction to surgical stress is the metabolic response to injury. Preventing stress and thus minimising this response represents the central mechanism around which the concept of enhanced recovery is based. This response encompasses all elements associated with surgery such as anxiety, fasting, tissue damage, haemorrhage, hypothermia, fluid shifts, pain, hypoxia, bed rest, ileus and cognitive imbalance. Such significant changes in metabolic and physiological homoeostasis represent a threat to the body and mind that need to be treated for a successful return to pre-operative conditions. Evidence suggests that this phenomenon, if left untreated, can lead to increased morbidity and mortality. Therefore, it makes sense to provide not only a rational basis for accelerated recovery but also to minimise the potential risk of organ dysfunction leading to complications and decreased long-term survival.[16]

The "stress response" is represented by hormonal and metabolic changes that result in haematological, immunological and endocrine responses, and its extent parallels the degree of tissue injury, being further amplified with post-operative complications. The interaction between the endocrine and inflammatory response is characterised by an elevation in counter-regulatory hormones (cortisol, growth hormone, glucagon and catecholamines) induced by activation of hypothalamic–pituitary–adrenal axis, and an initial predominance of pro-inflammatory cytokines followed by anti-inflammatory cytokines. Following tissue injury, the systemic inflammatory response is activated and mediated mainly by pro-inflammatory cytokines such as interleukins, IL-1 and IL-6. The effects of these mediators on target organs (such as hypothalamic thermoregulation or hepatic acute phase protein production) are modulated potentially by other components of the stress response (e.g. glucagon, cortisol or adrenaline). Local change impacts not only on the generalised inflammatory state but also on homoeostatic, metabolic and circulatory organs. An example of surgical stress-induced organ injury is represented by the occurrence of myocardial injury after non-cardiac surgery (MINS). MINS is where myocardial injury occurs causing a raised peak troponin T level of > 0.03 ng/ml (even without symptoms or a full definition of myocardial infarction) and it is an independent predictor of 30-day mortality.[17] In a recent large

cohort study of over 15,000 patients, 8.0% of patients suffered MINS with around 58% of these patients not fulfilling the universal definition of myocardial infarction and only 15.8% of patients with MINS experienced an ischaemic symptom. Although it is not known which ERAS elements can specifically reduce MINS, it has been recently demonstrated that when all the ERAS elements are used cardiovascular complications are reduced.[18]

The more extensive the surgical wound, internal organ manipulation and tissue dissection, the greater is the stress response. This concept not only applies to physiological/metabolic changes but also to changes in the innate immune system. This combination of catecholamine release and hyper-inflammation followed by immunosuppression can contribute, among other things, to a state of insulin resistance.[19,20]

A main reason for the effectiveness of the ERAS protocols is that many of the different treatments building the protocol reduce the stress responses to the injury caused by the operation and thus help to maintain homoeostasis.

Metabolic homoeostasis

Normal metabolism is governed by anabolic and catabolic hormones in interplay. Any major injury including surgery disrupts metabolic homoeostasis and cause insulin resistance. Insulin resistance can be defined as a condition, whereby a normal concentration of insulin produces a subnormal biological response.[19] Studies have demonstrated a significant correlation between the degree of the patient's insulin sensitivity on the first post-operative day and length of hospital stay ($r = 0.53$, $P = 0.0001$).[20] In a multifactorial analysis, the degree of insulin resistance, the magnitude of surgery and blood loss were the three independent factors explaining more than 70% of the variation in length of stay. More importantly, a significant association was shown between the magnitude of insulin resistance and complications. For every decrease in intraoperative insulin sensitivity by 20%, the risk of serious complications was more than doubled after open heart surgery.[21]

The relevance of insulin resistance to outcomes is also reflected by the clinical problems associated with its metabolic sequelae, the catabolic changes in glucose and protein metabolism also known as "diabetes of the injury". In non-diabetic patients undergoing major abdominal procedures, blood glucose (BG) values > 7 mmol/l are frequently observed. Evidence is mounting that hyperglycaemia is a predictor of mortality and complications, and that even a moderate increase in blood glucose may be associated with a worse outcome.[22–24] Patients with fasting blood glucose concentrations > 7 mmol/l or random blood glucose concentrations > 11.1 mmol/l on general surgical wards showed a 18-fold increased in-hospital mortality, a longer hospital stay and a greater risk of infection.[25] Post-operative protein catabolism is characterised by a net loss of functional and structural body protein. Metabolically healthy patients lose between 40 and 80 g of nitrogen after elective open abdominal operations, equivalent to 1.2–2.4 kg wet skeletal muscle.[26] Also, protein losses after abdominal surgery are 50% greater in insulin resistant patients than in those who are not.[27] More recent studies indicate a linear relationship between insulin sensitivity and protein balance in parenterally fed patients undergoing open heart surgery.[28] Loss of lean tissue delays wound healing, compromises immune function and diminishes muscle strength. The ensuing muscle weakness inhibits coughing, impedes mobilisation and prolongs mechanical ventilation if patients are on intensive care thereby complicating convalescence and causing morbidity.

Subjects with altered metabolic and inflammatory states such as elderly, diabetics and patients with cancer undergoing surgery can be exposed to a greater stress response, profound catabolic state as result of poor reserve, thus leading to post-operative complications and delayed functional recovery.[29–31]

Plasma glycosylated haemoglobin A (HbA1c) is an indicator of blood glucose control over the previous 3–4 months. Observations made in 273 diabetic and non-diabetic patients undergoing open heart surgery demonstrated a significant correlation between the quality of pre-operative glycaemic control as reflected by HbA1c levels and insulin sensitivity during cardiac surgery ($r = 0.527$, $P < 0.001$).[21] In addition, diabetic patients with HbA1c > 6.5% had a greater incidence of major complications ($P = 0.010$),

and minor infections ($P = 0.006$). Such patients received more blood products, and spent more time in the ICU ($P = 0.030$) and the hospital ($P < 0.001$) than metabolically normal patients.[21] These findings are in agreement with the results of other observational studies indicating worse outcomes after cardiac, abdominal and vascular procedures in the presence of increased HbA1c concentrations.[32–34]

ERAS interventions reducing insulin resistance

Several ERAS interventions are directed to reduce surgical stress and modulate perioperative insulin sensitivity directly and indirectly.

Pre-operative carbohydrate loading and adherence to pre-operative fasting guidelines

The idea of pre-operative carbohydrate treatment instead of overnight fasting came from animal studies showing that coping with stress is much improved if animals sustain trauma in the fed rather than fasted state.[35] Overnight treatment with intravenous glucose was shown to attenuate the decrease in muscle insulin sensitivity.[36] A similar effect was later shown for oral carbohydrates solutions tailored for pre-operative use.[37] The administration of such pre-operative oral carbohydrates raises insulin sensitivity by 50%,[38] and this carries through to the post-operative period resulting in 50% less insulin resistance. Carbohydrate loading also shifts cellular metabolism to a more anabolic state.[39] This allows for better use of any nutritional care post-operatively, with less risk of hyperglycaemia and improved retention of protein and preservation of lean body mass.[40] Studies conducted in relatively small patient populations suggested better outcomes with pre-operative complex carbohydrates given orally up to 2 h before anaesthesia and surgery,[41,42] However, a meta-analysis[43] and a recent Cochrane analysis[44] of all available data from randomised controlled trials suggest that in major abdominal surgery there is clinical impact as evidenced by faster recovery[43,44] (reduced length of stay by 1–1.5 days[43]). However, for minor surgery the benefit is mainly in patient well-being,[41] and in other types of surgeries the data remain sparse.[44] Many National and International Anaesthetic Societies recommend a 6-h pre-operative fast for solids and a 2-h fast for clear liquids, including carbohydrate drinks.[44–47]

Epidural anaesthesia

Another way of minimising post-operative insulin resistance is to use epidural anaesthesia. Ample evidence has accumulated in open surgery to identify the peripheral and central nervous system as a common pathway triggering the catabolic responses to tissue trauma. Blockade of these pathways by epidural anaesthesia and local anaesthetic blocks prevents the increase in circulating counter-regulatory hormones, thereby minimising insulin resistance and limiting protein catabolism[48] and hyperglycaemia.[49] The physiological effects of epidural anaesthesia may serve as a rationale for improved respiratory and cardiovascular outcomes after general, urological and vascular procedures as reported by meta-analyses and randomised controlled trials.[50,51]

Early post-operative feeding

A further additional potentially beneficial way to maintain metabolic homoeostasis is early feeding. Early recommencement of post-operative nutrition has been shown to benefit the patient.[52] However, most of the available data are from patients undergoing surgery in a traditional care programme, and very little is known about the effects of nutrition in a modern ERAS programme. One small study showed that after major colorectal surgery, in patients given pre-operative carbohydrates and thoracic epidural anaesthesia, complete enteral feeding initiated immediately after the operation normalised glucose levels and was associated with abolition of the catabolic response to surgery such that there was no net loss of body nitrogen (protein).[53] This suggests that it is possible to overcome most of the metabolic response to injury when post-operative feeding is combined with pre-operative carbohydrates and epidural anaesthesia.

Glycaemic control

The therapeutic administration of insulin is an obvious choice to overcome perioperative

insulin resistance and improve outcome. Normoglycaemia and whole body protein stores can be preserved by insulin therapy suggesting that insulin sensitivity rather than insulin responsiveness is reduced during and after surgery.[54] Although the safety and efficacy of glucose control in the ICU has been debated, trials have consistently shown that in post-operative patients[55] and in trauma patients[56] improved glucose control with insulin in the intensive care situation has proven beneficial by avoiding complications as long as the deleterious effects of hypoglycaemia are avoided. In the ward situation, intensive insulin treatment is more dubious and hard to control and, therefore, measures should be taken to minimise the insulin resistance and thereby avoiding the need of insulin.[53]

Magnitude of surgery and homoeostasis

Minimising the total surgical injury is the principal aim of minimally invasive surgery (MIS), and with optimal surgical techniques the benefits are not just from the reduction in wound size. This concept can be categorised into primary and secondary injury due to surgery. The primary injury is direct trauma to the abdominal wall or tissue damage from mobilisation of tissues or trauma to organs themselves. There is also indirect injury during surgery from bleeding or the physiological effects from anaesthetic techniques (intermittent positive pressure ventilation, drugs causing local vasomotor changes causing local blood flow changes) and the physiological effects of patient positioning combined with the abdominal pressure of the CO_2 pneumoperitoneum. The rationale behind minimising the access wound in particular is to reduce the activation of neuro-humoral pathways that affect recovery adversely. Reducing neuro-humoral stimulation may be achieved by reducing access trauma and internal trauma associated with the surgery.

Trauma to the abdominal wall may be reduced by changing the orientation of the incision such that it traverses fewer myotomes and dermatomes. Where open surgery is performed, transverse incisions may reduce post-operative pain and improve outcomes but the evidence for this is not clear.[57–59] The length of the access incision can be reduced using laparoscopic techniques that will reduce both the total additive length of the incisions and the maximum length of any one incision. Additionally, modern ports used for access work by splitting muscle fibres rather than dividing them, which is also less traumatic.

The intra-abdominal part of the operation is usually similar whether performed with open access or laparoscopically, but differs in a number of ways which might reduce trauma. This is witnessed by good evidence that overall blood loss is less[60] and adhesions are reduced following laparoscopic colorectal surgery.[61] A number of factors may contribute but the reduction of the size of peritoneal injury, the reduced serosal injury and the reduced blood loss will all reduce the tendency to form adhesions. The use of modern energy sources such as ultrasonic technology may also be a factor both in reducing blood loss but also reducing the collateral damage associated with other techniques. The techniques that have been developed with laparoscopic surgery also dictate the necessity to dissect carefully within bloodless plains where possible which may have a benefit in reducing collateral injury and reducing stimulation. This results in a reduction in secondary injury reducing the cytokine, hormonal and neural responses to surgery. The benefits of MIS are further enhanced by reducing consequential problems from fasting and immobilisation as there is a more rapid return of gut function and improved mobilisation.

The benefits from using MIS has to be balanced against the fact that to perform MIS the carbon dioxide (CO_2) pneumoperitoneum and patient position may have detrimental physiological effects which can be compounded if the duration of surgery is long. The initiation of CO_2 pneumoperitoneum triggers a sympathetic response and major changes in blood flow and respiratory mechanics. In fluid optimised patients, there is a rise in aortic afterload with resulting decrease in stroke volume and resultant reduction in oxygen delivery which can affect outcome.[62] This response usually lasts for 20–25 min until adaptation occurs but in some patients cardiac output remains low.[55] Studies to look at reducing the physiological impact of CO_2 pneumoperitoneum by using special ports

or deep neuromuscular block to facilitate good surgical exposure at lower pressures are ongoing.

Such graded interaction between minimal access surgery and ERAS is reflected in an additive effect in reduction of length of stay.[63] Thus MIS with its reduction in both primary and secondary injury has become a major component of ERAS.

Surgery and fluid balance

Following the initiation of injury, the release of catabolic hormones and inflammatory mediators facilitate salt and water retention to preserve intravascular volume, maintain blood pressure and vasoconstriction, and provide gluconeogenic substrates for metabolism and cell function. Body temperature decreases to minimise oxygen utilisation, and blood is shunted away from "non-vital" organs such as the gut, skin and muscle to maintain perfusion in vital organs like the heart, brain and kidney. Gene and protein expression of mediators of inflammation and insulin resistance, such as IL-6, AKT-1, FOXO-1, and PDK4 are increased within hours of the incision at the site of the injury (rectus abdominis muscle) and, to a lesser extent, distant from the site of the injury (vastus lateralis muscle).[64] There is also a consistent suppression of muscle mitochondrial complex activity and a decrease in ATP production rates over the same time period.[65] These changes are associated with an increase in intestinal permeability. Blood rheology is also altered with the initiation of a hypercoagulable state.

Teleologically, mammals have developed very efficient mechanisms to conserve salt and water in the face of fluctuations in water supply, scarcity of salt and reductions in plasma volume. On the other hand humans have not, until recent times, been exposed to salt excess and our mechanism for excreting this is correspondingly inefficient, depending on a slow and sustained suppression of the renin–angiotensin–aldosterone axis.[66,67]

Salt and water overload has been shown to impact on anastomotic integrity. Furthermore, ileus and increasing post-operative complications leading to prolonged hospital stay have been reported when maintenance of patients in a state of near-zero fluid balance is not achieved.[66,68] Generally, it has been shown that post-operative complications are increased when the weight gain in the post-operative period exceeds 2.5 kg (indicative of a 2.5 l cumulative fluid overload).[69]

The maintenance of fluid and electrolyte balance and tissue perfusion is achieved directly with several modalities within the ERAS programme and indirectly by overall modulation of the hormonal and inflammatory response. The principle of maintaining a patient in the zone of normovolaemia is to maintain a normal intravascular volume and avoid gaining weight due to excessive administration of fluid. Adequate preoperative hydration and avoidance of bowel preparation aim to keep the patient close to normovolaemia prior to surgery. Physiological interventions during anaesthesia such as intermittent positive pressure ventilation, vasoactive drugs and regional anaesthetic techniques can all affect vasomotor tone and intravascular volume. Due to the venous capacitance vessels, there is a range (sweet spot) within which normovolaemia, cardiac output and tissue perfusion can be adequately maintained. The experienced anaesthesiologist can keep the patient in this zone of normovolaemia throughout the operative and immediate post-operative periods. The use of additional monitoring devices such as pulse pressure variation (PPV), stroke volume variation (SVV), oesophageal Doppler and pulse contour wave analysis can all provide the anaesthesiologist with additional useful information to help guide fluid therapy, even though routine use of advanced hemodynamic monitoring and cardiac output optimisation has not shown to consistently improve post-operative outcomes.[70–73] This is more important when the physiological situation is challenging such as haemorrhage, poor cardiac function or vasodilatation secondary to drugs, regional analgesia or sepsis. Optimal control of intravascular volume, cardiac output and oxygen delivery combined with perfusion pressure maintains optimal oxygen and nutrient delivery to the cells as well as reducing extracellular fluid flux. Maintenance of normothermia maintains central and peripheral perfusion and effective circulatory volume. This makes it easier for the anaesthesiologist to avoid the patient becoming

relatively hypovolaemic with resultant hypoperfusion of tissues with development of acidosis and lactataemia. The early establishment of oral intake of fluids as soon as possible after surgery allows the body to control homoeostasis.

Figure 2 shows 2 patient pathways with fluid shifts during and immediately after surgery. One patient is in an ERAS surgical protocol and the other in a traditional surgical pathway. The patient undergoing surgery within a traditional pathway has prolonged starvation and bowel preparation causing dehydration. The patient is hypovolaemic prior to the start of surgery and at the start anaesthesia, and intermittent positive pressure ventilation and drugs have a further negative effect causing splanchnic hypoperfusion. Intravenous fluid infusion restores the intravascular volume, however the prolonged continuation of intravenous fluids post-operatively for several days can lead to relative hypervolaemia and gut oedema with resultant ileus. The patient within the ERAS programme starts surgery within the 'green zone' of normovolaemia and is maintained there by the anaesthesiologist monitoring stroke volume and keep intravascular volume optimised which in turn reduces fluid shifts. Intravenous fluids are maintained at appropriate rates in the immediate post-operative period to maintain normovolaemia, but are then stopped with the commencement of oral intake thus avoiding salt and water overload. It is obvious that the controversy on perioperative fluid balance will continue as more research is carried out in patients at risk where careful administration of fluids and appropriate monitoring are taken into account.

Surgery and gut dysfunction

Major abdominal surgery induces an immunoinflammatory response, which is accompanied by the production of reactive oxygen species (ROS) at the site of injury causing direct cellular injury by damaging lipids, proteins and DNA. Similarly, the hypothalamic peptide corticotropin-releasing hormone appears to interact with the inflammatory components and inhibit bowel function. The resulting impaired vascular permeability together with excessive fluid administration can lead to fluid overload, interstitial oedema and therefore delayed recovery of gastrointestinal function and impaired anastomotic healing.[68]

The causation of post-operative ileus is multifactorial and a number of risk factors have been identified (Fig. 3). These include increasing age, male gender, low pre-operative serum albumin, acute and chronic opioid use, previous abdominal surgery, pre-existing airways and vascular disease, long duration of surgery, emergency surgery, blood loss and salt and water overload. Most of these factors increase the inflammatory response, and inflammation and oedema play a major role in reducing intestinal smooth muscle contractility.[74] ERAS principles are aimed at reducing perioperative stress and inflammation and, hence, can reduce the duration of ileus and accelerate recovery of gut function post-operatively.

A number of strategies have been suggested to prevent post-operative ileus and some are more effective than others. These have been reviewed extensively recently and are summarised in Table 1.[74]

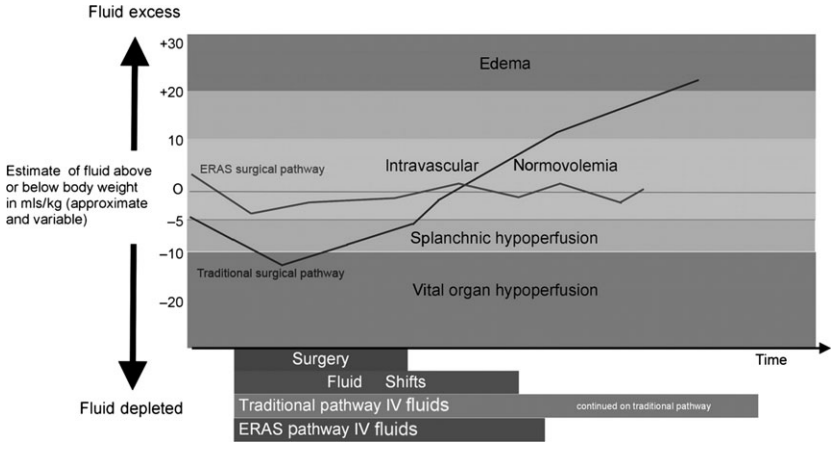

Fig. 2. Perioperative fluid administration with and without an ERAS surgical pathway: risk of perioperative fluid excess and tissue hypoperfusion.[104] Reproduced from Minto G et al. with permission.

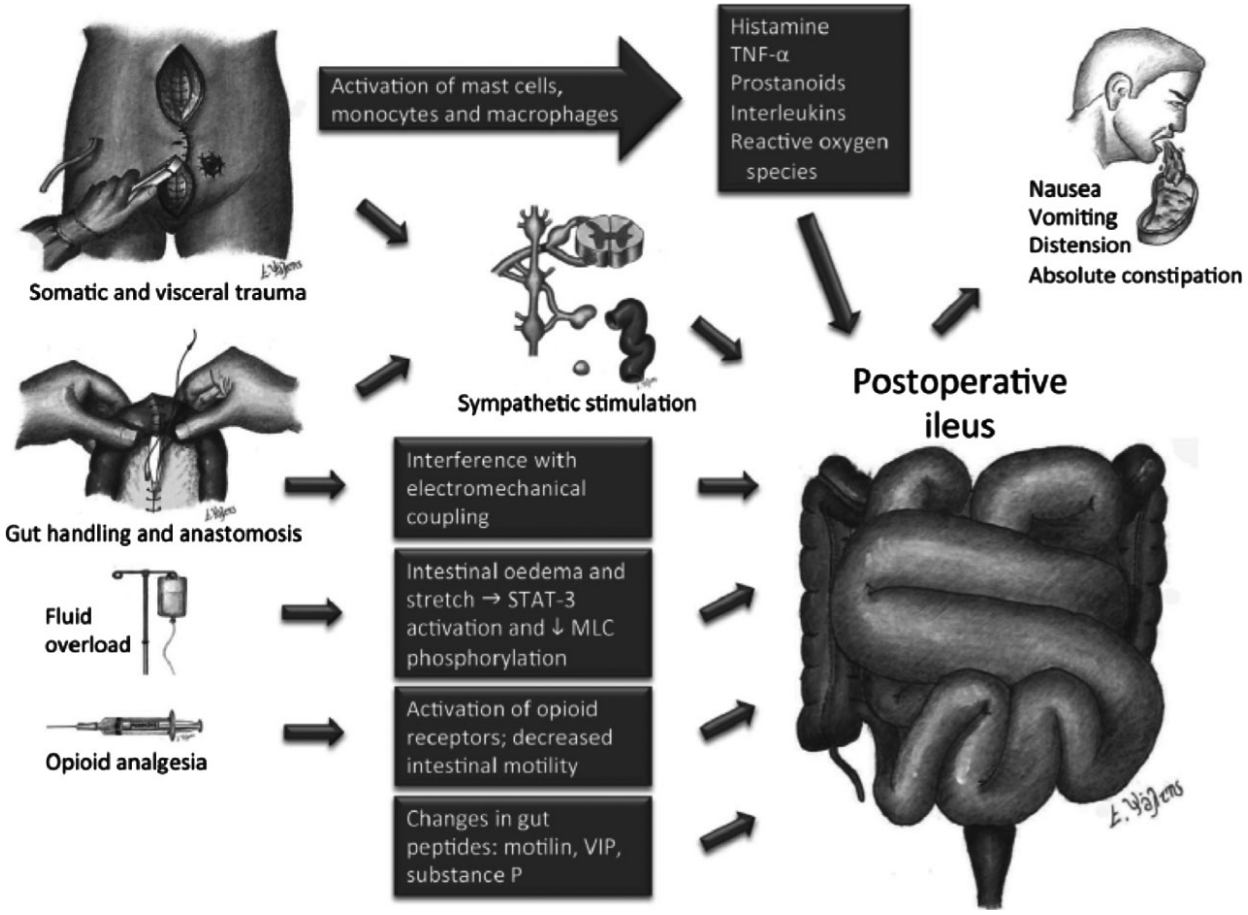

Fig. 3. Pathogenesis of post-operative ileus. MLC, myosin light chain; STAT, signal transducer and activator of transcription; TNF, tumour necrosis factor; VIP, vasoactive intestinal polypeptide. From Bragg et al. with permission.[74]

Alvimopan is a peripherally acting μ-opioid receptor antagonist, which does not cross the blood–brain barrier readily. A meta-analysis examining the effect of alvimopan vs. placebo on POI after major abdominal surgery found that alvimopan accelerated recovery of gastrointestinal function by 1.3–1.5 days at a dose of 12 mg/day and 6 mg/day respectively.[75] The time to readiness for discharge was also reduced correspondingly.[75] However, alvimopan is expensive ($1000 for 15 doses) and is not readily available outside the United States.

Surgery and anaesthesia are responsible for initiating nausea and vomiting in the post-operative period. More specifically, abdominal distension, bowel manipulation, intracellular fluid overload, and opioids stimulate peripherally (gut) and centrally located receptors that activate the central coordinating site for nausea and vomiting which is located in an ill-defined area of the lateral reticular formation in the brain stem.[76,77] This "vomiting centre", as it is traditionally called, is not so much a discrete centre of emetic activity as it is a "central pattern generator" (CPG) that sets off a specific sequence of neuronal activities throughout the medulla to result in vomiting.[78–80] A particularly important afferent is the chemoreceptor trigger zone (CTZ), which is located at the base of the fourth ventricle in the area postrema, outside the blood–brain barrier, and plays a role in detecting emetogenic agents in the blood and cerebrospinal fluid (CSF).[78] Five distinct receptor mechanisms have been identified in the CTZ that are involved in nausea and vomiting. They are serotonergic, dopaminergic, histaminergic, muscarinic and neurokinin-1 type. A variety of different pharmacological agents, acting on one

Table 1 Strategies to prevent post-operative ileus. From Bragg et al.[74] with permission.

Intervention	Mechanism	Benefit
		++
Salt and fluid overload	↓ gut oedema and stretch	±
Carbohydrate loading	↓ insulin resistance	–
Routine nasogastric tubes	Prophylactic drainage of stomach	+
Intravenous lidocaine	Anti-inflammatory; opioid-sparing	+
Coffee	Stimulatory effect	+
Chewing gum	Stimulatory effect	++
NSAIDs	Anti-inflammatory; opioid-sparing	++
Early enteral nutrition	Anabolic; ↓ insulin resistance; stimulatory	++
ERPs	Multimodal effect	++
Laparoscopic surgery	↓ tissue trauma; ↓ bowel handling; ↓ inflammatory reaction	++
Alvimopan	μ-opioid receptor antagonist	++
Mid-thoracic epidural anaesthesia	↓ inflammatory response ↓ sympathetic stimulation ↓ opioid requirement	+/±
Early mobilisation	? anabolic effect	+
Nicotine	Colonic prokinetic	+
Daikenchuto	Anti-inflammatory on acetylcholine receptors	+
Magnesium sulphate	Anaesthetic effect	±
Prokinetics	Prokinetic effect	

or more of the five major neurotransmitter categories are routinely used for the prophylaxis and/or treatment of PONV.[81]

Opioids, although not neurotransmitters, may have a significant effect on PONV, exerting both excitatory and inhibitory effects on the gastrointestinal system (e.g. inhibition of gastrointestinal motility). There are at least three different types of opioid receptors – μ, d and k. Exogenous opioid receptor agonists (e.g. morphine) affect intestinal motility by modulating cholinergic transmission. When administered peripherally, exogenous opioid receptor agonists decrease gastrointestinal motility and delay gastric emptying by inhibiting central μ-receptors.[82]

Risk factors for PONV are based on characteristics relating to the patients, anaesthetic or type of surgery. Specific risk factors for PONV in adults are female gender, history of PONV or motion sickness, use of opioids and non-smoking status. Although the relationship between patient-related risk factors and PONV are clear and well studied, such a relationship with type and duration of surgery is less clear. Nevertheless, a simplified risk scoring system for PONV incorporating the four risk factors have good predictability and is recommended for risk-based PONV prophylactic therapy.[81]

Surgery and nociception

Surgical incision and manipulation of tissues lead to cell disruption releasing a variety of intracellular chemical mediators. These include potassium, adenosine, prostanoids, bradykinin, nerve growth factors, cytokine and chemokine which activate and sensitise (peripheral sensitisation) peripheral nociceptors Aδ and c-fibres to mechanical stimuli (primary hyperalgesia). These pro-inflammatory substances and the release of substance P and calcitonin gene-related peptide from the peripheral branches of nociceptors also sensitise silent Aδ nociceptors in the adjacent non-injured tissues (secondary hyperalgesia). Repeated and prolonged stimulation of peripheral nociceptors in the injured area and in the surrounding non-injured tissues lead to an increase firing of neurons at the level of the dorsal horn of the spinal cord, mediated by the activation of Na-methyl-D-aspartate (NMDA) receptors (central sensitisation). Clinically, these pathophysiological changes could manifest with hyperalgesia, allodynia, and even persistent postsurgical pain. Descending sympathetic inhibitory pathways also play an important role at the level of the spinal cord by modulating transmission of noxious inputs. The response to nociception contributes to activate and potentiate the stress response associated with surgery. Activation of the hypothalamic–pituitary–adrenal axis (HPA), sympathetic stimulation and systemic release of pro-inflammatory cytokines are major determinants of post-operative insulin resistance, that if not attenuated potentially lead to multiorgan dysfunction (Fig. 4). Acute surgical pain can, therefore, be

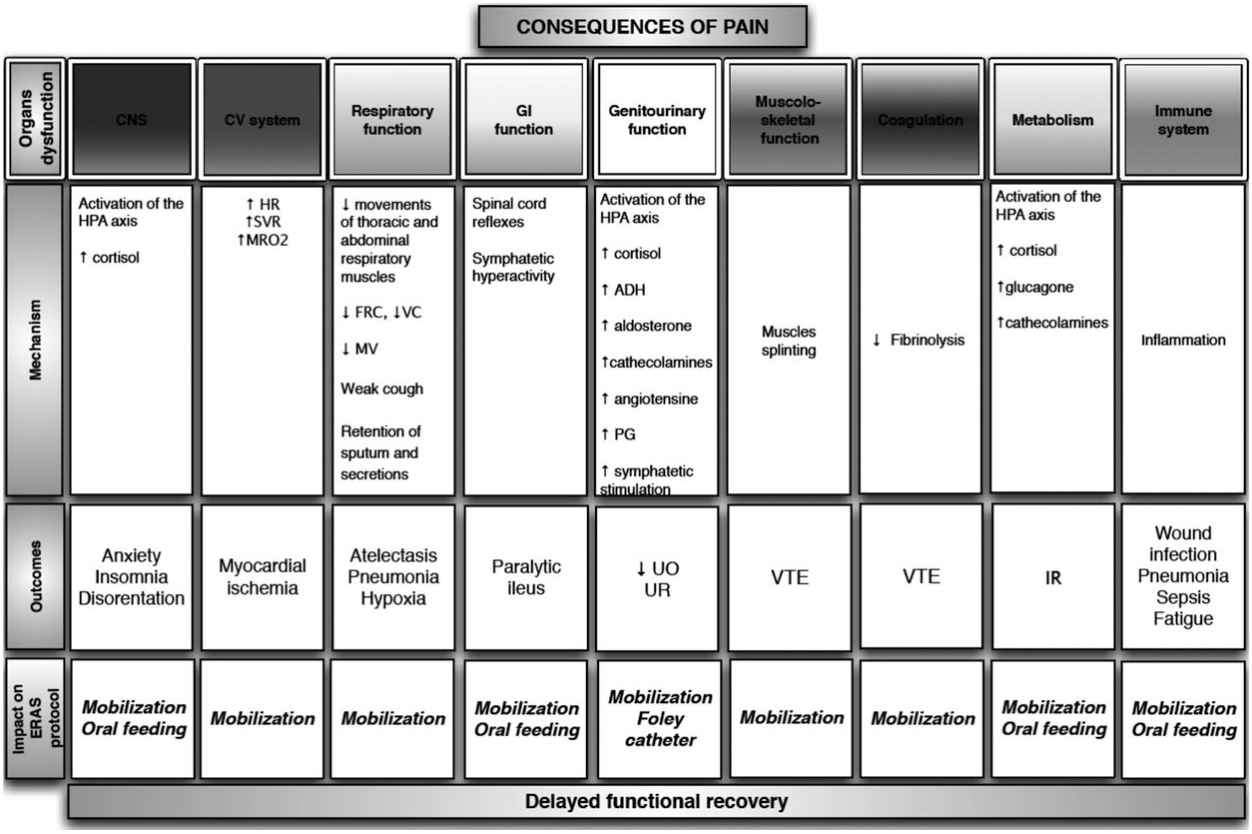

Fig. 4. Post-operative pain: physiological consequences and impact on outcomes and ERAS protocol. CNS, Central Nervous System; HPA axis, Hypothalamic–Pituitary–Adrenal axis; CV, Cardiovascular; HR, Heart Rate; SVR, Systemic Vascular Resistance; MRO2, Metabolic Rate of Oxygen; FRC, Functional Residual Capacity; VC, Vital Capacity; MV, Minute Ventilation; GI, Gastrointestinal; ADH, Antidiuretic Hormone; PG, Prostaglandins; UO, Urinary Output; UR, Urinary Retention; VTE, Venous Thromboembolism; IR, Insulin Resistance. Reproduced from Cologne K et al. with permission.[106]

somatic, visceral or neuropathic depending on the type of surgery and on the surgical approach.[83,84] The scientific rationale for multimodal analgesia is based on the multifactorial nature and complexity of surgical pain pathways. The purpose of multimodal analgesia is to control pain with different classes of medications acting on multiple sites.[85] In the context of the ERAS programme, the adaptation of multimodal analgesic strategies aims not only to improve post-operative pain control and reduce surgical stress but also to attenuate the multiorgan dysfunction induced by unrelieved pain, reduce opioid side effects, facilitate early resumption of oral diet and early mobilisation and ultimately accelerate surgical recovery (Fig. 4). Ten years ago ERAS programmes relied extensively on thoracic epidurals and NSAIDs as the cornerstones of analgesia. For colorectal surgery at least, there has been a sea change away from open surgery and towards laparoscopic techniques whenever possible. Equally, there have been concerns raised about a possible adverse influence of NSAIDs on anastomotic integrity.[86] These two factors have led to the increased use of spinals/TAP blocks or intravenous lidocaine and decreased use of epidural anaesthesia/NSAIDs.[87,88] It has to be said that while the physiological effects of epidural blockade on surgical stress have been well validated, the same cannot be said for lidocaine i.v. infusion and local anaesthetics techniques such as TAP blocks.

Surgery and cognitive dysfunction

Surgical trauma provokes a neuroinflammatory response resulting in either transitory and rever-

sible or persistent impairment of cognition.[89] While some patients develop post-operative delirium (POD), characterised by inattention, disorganised thinking and altered level of consciousness, others develop post-operative cognitive dysfunction (POCD) which is chronic by nature and characterised by deficit in attention, concentration, executive function, verbal memory, visuospatial abstraction and psychomotor speed.

The international study on post-operative cognitive dysfunction (ISPOCD 1) study published in the lancet in 1998 demonstrated long-term POCD in elderly patients undergoing non-cardiac surgery.[90] However, the second study published in 2003 (ISPOD2) found no significant difference in the incidence of cognitive dysfunction 3 months after either general or regional anaesthesia.[91] Accordingly, there is no evidence to suggest any causative relationship between general anaesthesia and long-term POCD.

A possible pathogenic mechanism is of inflammatory nature whereby pro-inflammatory cytokines increased significantly in the systemic circulation and the central nervous system.[92] Pre-existing factors can contribute to POCD, such as advanced age, metabolic syndrome, education, vascular dementia and attention deficit disorders. Sleep disruption, poor analgesia, anaesthetic medications such as benzodiazepines can further exacerbate POCD.

Due to the complexity of the pathogenic mechanism and the multifactorial nature of POD and POCD, attempts are made to identify vulnerable patients and interventions which promote resolution of neuroinflammation. In this context, strategies such as minimally invasive surgery, guiding anaesthetic depth with BIS monitoring,[93,94] adequate pain relief, limited use of benzodiazepines[95,96] and opioids, a quiet environment to facilitate sleep and accelerated discharge home have been proposed as effective measures which need to be confirmed in large trials.

Surgery and post-operative deconditioning

Prolonged bed rest for up to several weeks in hospital was standard surgical practice until the 1940s, probably originating from fears of wound infection or dehiscence and the idea that rest would promote tissue healing.[97] Individuals confined to bed experience a linear decline in exercise capacity, as a result of reduced maximal stroke volume and cardiac output with VO_2max decreasing at a rate of about 1% every 2 days.[98] Complications of prolonged bed rest include skeletal muscle atrophy and weakness, bone loss, decreased insulin sensitivity, thromboembolic disease, microvascular dysfunction, atelectasis and pressure ulcers.[99,100] The negative effects of bed rest can occur after a relatively short period. Decreases in insulin sensitivity can also be detected after as little as 3 days of bed rest; even just 1 day of physical inactivity (sitting) can reduce insulin sensitivity significantly.[101] In older patients, deconditioning occurs by day 2 of hospitalisation.[102]

Post-operative fatigue (POF) is a well-recognised condition characterised by tiredness, lack of concentration which can impact on patient's quality of life. It can occur for several weeks after abdominal surgery and the duration is related to the intensity of surgery.[103] It appears that cancer has some influence on the development of post-operative fatigue. Beside the reported unpleasant and distressing symptoms, objective measures of POF have been identified, such as increased exercise-induced heart rate, elevated production of pro-inflammatory cytokines, decline in cardiorespiratory effort, weight loss, muscle weakness and anorexia. Patients need more energy to perform a given physical task. The psychological aspects of POF have been studied in depth, and it appears that while early symptoms of fatigue can be due to somatisation, late fatigue is secondary to cognitive-behavioural factors. Pre-operative anxiety and depression has been reported to be predictive of the development of fatigue.

ERAS pathways are not specific in relation to the type of exercise to be conducted after surgery as there is no evidence at present to support the use of one plan over another. There is a need to emphasise the importance of an early structured mobilisation plan with daily written targets for time out of bed or distance walked, beginning as early as the day of surgery. POF has a multimodal aetiology and, therefore, requires multimodal intervention. Some improvement in POF has been reported with imple-

mentation of combining therapeutic strategies, however more data are required.

Conclusions

Understanding the pathophysiology of the surgical stress response enables clinicians to identify the therapeutic interventions which are incorporated into the ERAS pathway aiming at accelerating the recovery process by targeting some key elements, insulin resistance, disruption of homoeostasis and nociceptive stimulation. There is some evidence that the ERAS synergistic approach is effective and physiologically makes sense, although this is not always translated into clinical outcome. Many aspects need more clarification as the literature is conflicting as ERAS principles continue to evolve and more research is required. ERAS is evidence-based, however translation into clinical care is lagging. It requires continuing professional development, additional debate, interdisciplinary involvement, patient education and regular revalidation. Ultimately, ERAS can lead to major improvements in the quality of patient care, better patient outcomes as well as economic benefits for the whole health care system. This implies that anaesthesiologists play a crucial role in development and the deployment of the programme.

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